

Triglyceride Mobilization

Triglyceride Synthesis

Triglycerides are **three fatty acids** attached to a **3-carbon backbone**, glycerol. Triglyceride is what we call “fat.” It’s the fat in adipose; it’s the fat in your abdomen, and the fat of your mesentery. “Fat” should not be found anywhere other than liver and adipose; finding it in organs is pathological and having fat deposits in blood vessels is atherosclerosis. “Fat” is made by taking a **glycerol-3-phosphate** and attaching, one fatty acid chain to each carbon, **3 fatty acids**. The fatty acids are activated with CoA, then added to one of the carbons, one fatty acid chain per carbon.

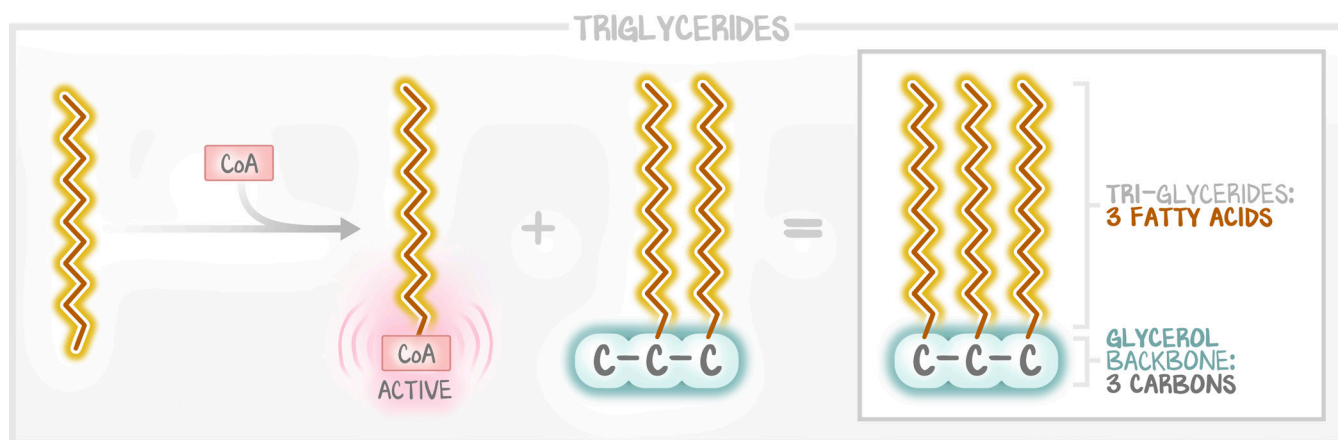


Figure 14.1: Triglycerides

The glycerol backbone is 3 carbons long. Each fatty acid chain is activated with acetyl-CoA and then attached to one of the carbons of the glycerol backbone.

Both adipose and liver make triglycerides, as in they assemble glycerol-3-phosphate and three fatty acids. Only the liver can synthesize new fatty acids. Both take 3 CoA-activated fatty acids and add them to glycerol-3-phosphate. Both make the final product, triglyceride. Both **use glucose** to make glycerol-3-phosphate. Glycerol-3-phosphate comes from DHAP, an intermediate step in glycolysis. In Metabolism #3: *Glycolysis* we assumed that fructose-1,6-bisphosphate becomes two glyceraldehyde-3-phosphate. For the purposes of glycolysis, that’s all we need to know. But in reality, glyceraldehyde-3-phosphate and DHAP are made. Now that PDH-TCA-ETC has slowed because of substrate-level inhibition, DHAP accumulates, and is shunted toward assembling triglycerides.

Only hepatocytes can **synthesize glucose** from glycerol (through DHAP and back, through the rest of gluconeogenesis). **Only hepatocytes** can **dispatch triglycerides** to the periphery—via **VLDL particles**. The liver sends the glycerol-3-carbon-backbone-plus-fatty-acids into the blood; the adipose tissue takes the three fatty acid chains and **sends back hepatic glycerol-3-phosphate**. Most of the glycerol-3-phosphate in the liver that assembles triglycerides comes back from the periphery. The adipose tissue has already made its own cytoplasmic glycerol-3-phosphate from the glycolysis of the circulating glucose. Adipose stores fat as triglycerides.

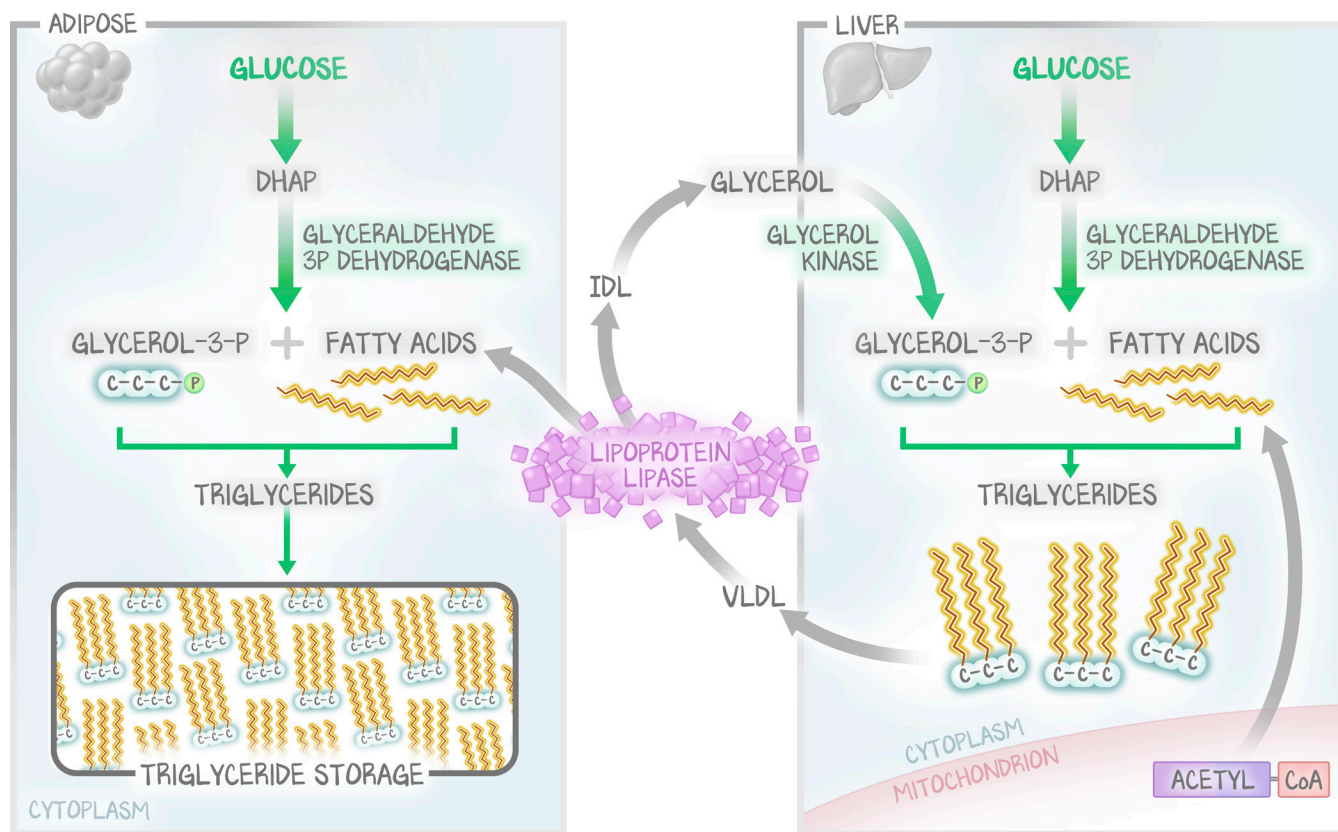


Figure 14.2: Lipid Storage

In the insulin-dominant state, the liver dispatches fatty acids to be stored by adipose tissue as triglycerides. Lipoprotein lipase takes the fatty acids from the triglycerides, and combines them with a different glycerol in the adipose to reform triglycerides. The glycerol backbone, having originated in the liver, is recycled to the liver.

The enzyme that liberates the three fatty acids from the VLDL particles into the adipose while returning the glycerol to the liver is **lipoprotein lipase**. Lipoprotein lipase is discussed in great detail later in this lesson.

Only hepatocytes can recycle glycerol. The glycerol that returns from the periphery after depositing the fatty acids at the adipose tissue is not phosphorylated. The liver is able to use **glycerol kinase** to recycle that glycerol back to the glycerol-3-phosphate required to make triglyceride.

Implications on Hormones

Adipose tissue is dependent on glucose to make its glycerol-3-phosphate. The **only way adipose** can make glycerol-3-phosphate is from glucose. To get glucose into the cell, adipose tissue, like skeletal muscle, is dependent on **insulin-activated GLUT4** transporters. Insulin binding causes preformed vacuoles with GLUT4 transporters to be inserted into the cell membrane, which lets more glucose into the adipose cell. Then the usual things happen—trapping with hexokinase, glycolysis, etc. Adipose therefore requires glucose-in-the-blood and for **insulin dominance** to store fat. This makes sense, of course, because when glucagon is dominant, we want to be mobilizing fatty acids back to the liver for oxidation for energy in between meals.

Hepatocytes can make fats or glucose. Hepatocyte **gluconeogenesis** can make the glucose that is released into the bloodstream for adipose tissues to use. However, because insulin will not be dominant, there'll be a small likelihood that the adipose will use that glucose for fat; adipose will use that glucose for energy (TCA-ETC). Adipose waits for glucose to be abundant (insulin-dominant) to store fat.

Hepatocytes synthesize fatty acids. Hepatocytes synthesize AND recycle glycerol-3-phosphate.

Hepatocytes assemble triglycerides.

LIVER ONLY	BOTH ADIPOSE AND LIVER
Synthesizes fatty acids	Assemble triglycerides
Synthesizes glucose	Disassemble triglycerides into fatty acids
Dispatches triglyceride	Synthesize glycerol-3-phosphate from glucose

Table 14.1: Functions of Adipocytes vs. Hepatocytes

Both tissues manipulate fatty acids and triglycerides, but be cautious what the limitations of each are. The liver synthesizes de novo, while the adipose tissue can only assemble and disassemble triglycerides.

Phospholipids

While not involved in metabolism of fatty acids or generating energy, **triglycerides** (glycerol with 3 fatty acids) are certainly structurally linked to glycerophospholipids. Phospholipids form the structure of our lipid bilayers, the cell membrane, and the membrane of organelles such as mitochondria and the nucleus. These phospholipids have the **same glycerol backbone** and the **same two fatty acid chains**, but on the third position they have a **phosphate + water-soluble group**. The water-soluble group is the **cytoplasmic-facing** side, while the two tails, made of the two chains of fatty acids, are hydrophobic and face inward. Why do we include this? Because **cholesterol** and **fatty acids are necessary to live**.

In calorie-rich, obese America, we see fat and cholesterol as “bad.” We’re going to talk about the physiology of fat—that is, why it’s good, and why we developed the system we did. For discussion, transport to 3,000 BCE when food was not plentiful, calories were not condensed and processed, and cholesterol and phospholipids were limited commodities.

Dietary Fat

Foods containing fat, with triglyceride, with **fatty acids attached to glycerol**, go into the intestine. We discuss this more in gastrointestinal physiology, but because the fatty acid chains are **hydrophobic**, the fats tend toward droplets of fat called **micelles**, lipophilic on the inside. In much the same way, when absorbed from the gut, the hydrophobic chains need to be carried, hidden from the water in the plasma. These particles have protein on the outside and lipid on the inside.

When a particle rich in triglycerides leaves the enterocyte into the lymph, that particle is called a **chylomicron**. Chylomicrons are cholesterol and triglyceride transport particles that are made in the intestine. Proteins involved with triglyceride mobilization are called **apo-proteins**. Chylomicrons come from the intestine, and the intestine apo-protein is **apoB48**. ApoB48 means “made by intestine.” ApoB proteins are “made by” tags. ApoB48 is intestine; apoB100 is liver.

As the chylomicron enters the blood it is further tagged with **apoC2**, and **apoE**. ApoE is a destination sequence, which says “go to the liver.” ApoC2 is another destination tag; apoC2 says “go to peripheral tissues.” The apoC2 and apoE tags were placed by circulating HDL. The apoC2 finds its target in

peripheral tissues, **peripheral lipoprotein lipase**, where the glycerol is cleaved and dispatched back to the liver while the released fatty acids are stored as triglyceride in the adipose cell.

What is left is a **chylomicron remnant**, now with little triglyceride and a bunch of cholesterol. It's sent to the liver for metabolism (apoE). There, the remnant is internalized and destroyed, and the cholesterol and whatever triglycerides are left over are processed by the liver.

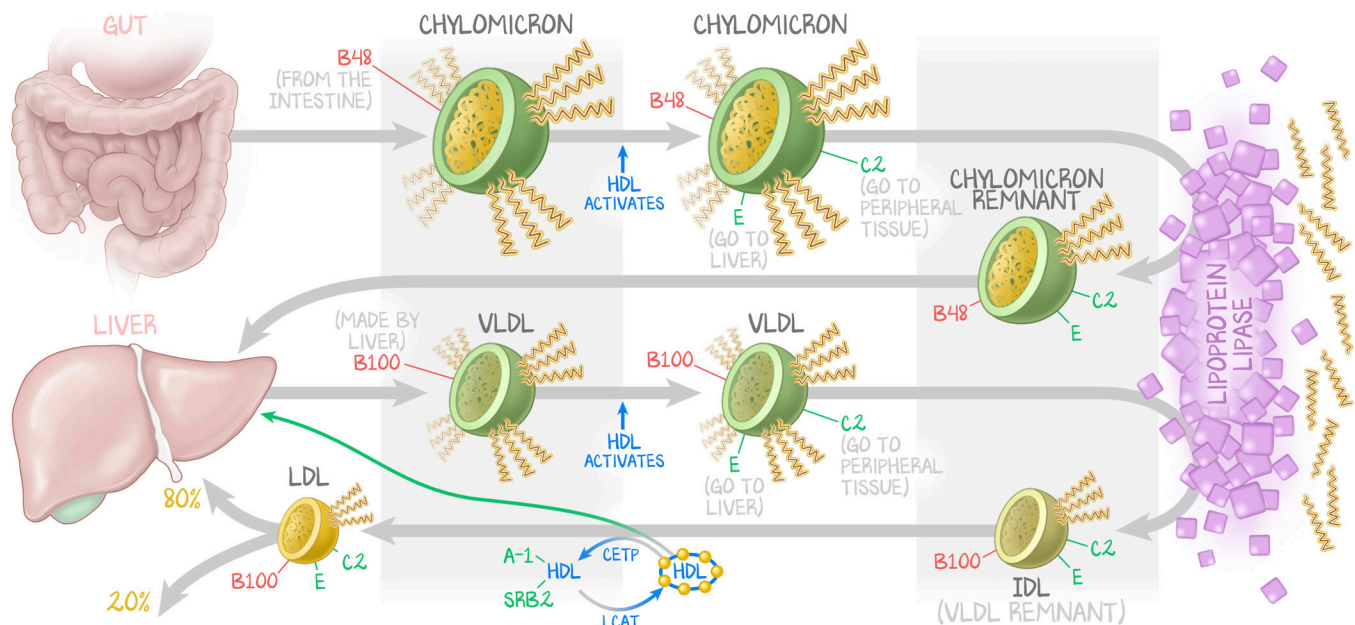


Figure 14.3: Dietary and Endogenous Fat

Notice the similarities of endogenous fat (VLDL, activation by HDL, lipoprotein lipase, remnant) and exogenous fat (chylomicron, activation by HDL, lipoprotein lipase, remnant). Then also notice the differences in fatty acid and cholesterol concentrations in each particle. Apoprotein B is the “from” tag, whereas apoprotein A and E2 are “to tags.”

Endogenous Fat

The liver manufactures a particle just like the chylomicron called a very-low-density lipoprotein. The **VLDL** is rich in triglyceride, just like the chylomicron, only it has less cholesterol. The VLDL has a “made from the liver” tag, an apoB protein, called **apoB100**. In the peripheral circulation, HDL marks the VLDL with destination tags: **apoC2** for the periphery and **apoE** for the liver, same as the chylomicron. These VLDLs go to the peripheral tissue, interact with lipoprotein lipase, give adipose the fatty acids for storage, and then are left with a VLDL remnant, called **IDL**.

Here’s where things get different between endogenous (liver) and exogenous (dietary) fat. The IDL particle is now mostly protein, its triglycerides delivered, and there are some cholesterol esters. Forget for a moment what you think you know about cholesterol. In a normal, healthy person, **cells need cholesterol**. **Cholesterol** makes the lipid bilayer fluid, and cell membranes are made of glycerol-backed fatty acids. When one cell stops using those materials (i.e., the cell dies) the body has a system of recovering those resources for later use. That system transfers the unused-cholesterol-left-over-in-the-periphery-from-dead-cells to other cells that need it (those expressing receptors for cholesterol) by having **HDL** pick it up **from the periphery** and **give it to IDL**. When HDL gives IDL that cholesterol, it becomes **LDL**. LDL then goes 80% to the liver for processing, 20% to the periphery to hand out the cholesterol that every cell needs.

But now, flash forward to 21st-century America. We have a different problem than “we need to recycle resources.” When LDL goes to hand out that much-needed cholesterol, the LDL particles find that no one wants any. All the cells are good, full up on cholesterol and lipids. So LDL just keeps circulating with all this cholesterol. It can go home when it gives away its cholesterol, but without anyone wanting any, LDL can’t go home. And when LDL circulates for too long, unable to give away its cholesterol, it gets oxidized, and drops some. The LDL gets tired of carrying so much cholesterol that no one wants and dumps it in the blood vessels. That leads to atherosclerosis. The HDL keeps trying to stack up that extra peripheral cholesterol, but it has nowhere to put it, except back on the already-overloaded LDL.

HDL Enzymes Named and Explained

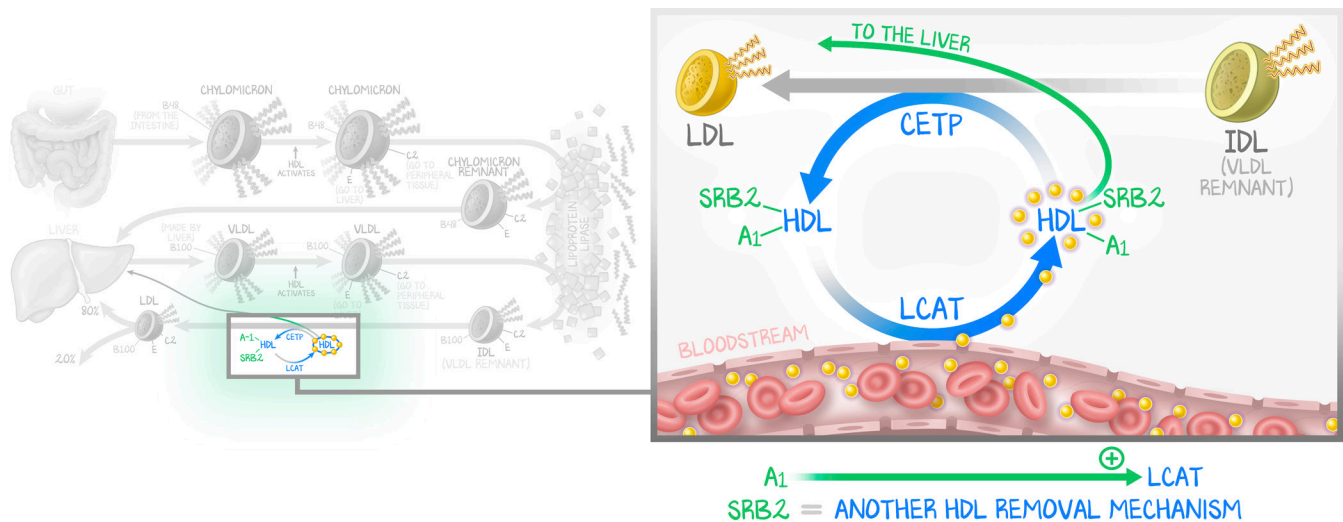


Figure 14.4: HDL and Cholesterol

Zoomed-in function of HDL cholesterol, which scoops up spilled cholesterol, then hands it off to the IDL (VLDL remnant), loading it up with cholesterol to be sent back to the liver as LDL.

HDL is able to pick up peripheral cholesterol using **LCAT** (lecithin-cholesterol acyltransferase).

The HDL apoprotein **A1**, an apo-protein only HDL has, activates LCAT to extract fatty acids from the periphery and add them to the HDL cholesterol. HDL hands off those fatty acids to IDL using **cholesterol ester transfer protein** (CESTP). HDL sweeps up the mess, and gives those much-needed resources to LDL to circulate and distribute; A1 activating LCAT, and CESTP giving LDL the cholesterol back. But HDL also has the ability to **actually move** the fatty acids it picks up itself. Using a **scavenger receptor SR-B1**, an HDL particle can bring the cholesterol directly back to the liver for processing. Unlike the LDL-receptor, which causes endocytosis, the SR-B1 of HDL is the same handoff mechanism CESTP was.

In current society, the HDL picks up spilled LDL cholesterol, not dying cells’ cholesterol. HDL gives it back to LDL. And though LDL goes around trying to give away the cholesterol, everyone has had their fill. So the cycle of HDL pick-up, hand-off to LDL, and LDL spills repeats. And, in the case of atherosclerosis, the LDL spilling has been winning.